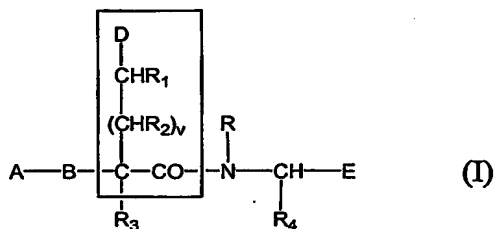


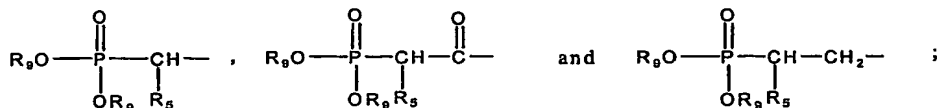
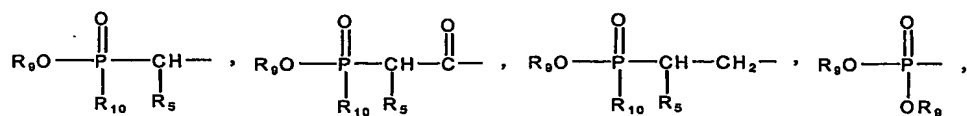
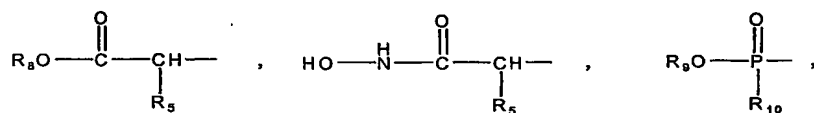
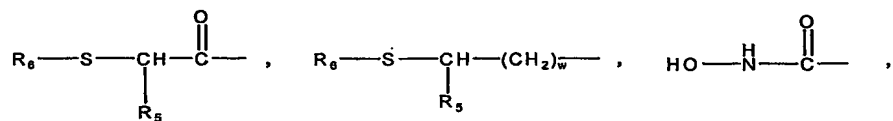
**CLAIMS:**

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



5 wherein:

A is a zinc ligand or zinc ligand bearing moiety selected from the group consisting of:



B is  $\begin{array}{c} \text{R}_{11} \\ | \\ -\text{N}- \end{array}$ ,  $-\text{CH}_2-$  or absent;

R is hydrogen or lower alkyl ;

R<sub>1</sub> is hydrogen or lower alkyl ;

R<sub>2</sub> is hydrogen, or lower alkyl;

- 5 R<sub>1</sub>, when v=1, may be connected to the carbon bearing R<sub>2</sub> to form an alkylene bridge of 1 carbon atom, representing with the carbon atom to which it is attached a cyclopropane ring;

R<sub>2</sub>, when v=1, may be connected to the carbon bearing R<sub>1</sub> to form an alkylene bridge of 1 carbon atom representing with the carbon atom to which it is attached a cyclopropane ring;

- 10 R<sub>3</sub> is hydrogen or lower alkyl;

R<sub>1</sub>, when v=1, may be connected to the carbon bearing R<sub>3</sub> to form an alkylene bridge of 1 carbon atom, representing with the carbon atom to which it is attached a cyclobutane ring;

- 15 R<sub>3</sub>, when v=1, may be connected to the carbon bearing R<sub>1</sub> to form an alkylene bridge of 1 carbon atom, representing with the carbon atom to which it is attached a cyclobutane ring;

R<sub>1</sub> and R<sub>3</sub>, when v=1, may be connected together to form an alkylene bridge of 2 carbon atoms representing with the carbon atoms to which they are attached a cyclopentane ring;

- 20 R<sub>1</sub> and R<sub>3</sub>, when v=0, may be connected together to form an alkylene bridge of 3 carbon atoms representing with the carbon atoms to which they are attached a cyclopentane ring;

- 25 R<sub>1</sub> and R<sub>3</sub>, when v=0, may be connected together to form an alkylene bridge of 4 carbon atoms representing with the carbon atoms to which they are attached a cyclohexane ring;

R<sub>1</sub> and R<sub>3</sub>, when v=1, may be connected together to form an alkylene bridge of 3 carbon atoms representing with the carbon atoms to which they are attached a cyclohexane ring;

- 30 R<sub>4</sub> is lower alkyl, substituted lower alkyl, cycloalkyl-(CH<sub>2</sub>)<sub>w</sub>-, aryl-(CH<sub>2</sub>)<sub>w</sub>-, substituted aryl -(CH<sub>2</sub>)<sub>w</sub>- or heteroaryl-(CH<sub>2</sub>)<sub>w</sub>-;

R and R<sub>4</sub> may be connected together to form an alkylene bridge of 3 carbon atoms representing with the nitrogen and carbon atoms to which they are attached a pyrrolidine ring;

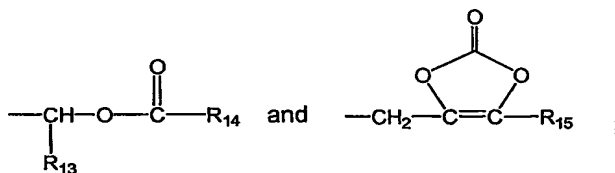
5 R and R<sub>4</sub> may be connected together to form an alkylene bridge of 4 carbon atoms representing with the nitrogen and carbon atoms to which they are attached a piperidine ring;

R<sub>5</sub> is hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl-(CH<sub>2</sub>)<sub>x</sub>-, aryl-(CH<sub>2</sub>)<sub>x</sub>-, substituted aryl-(CH<sub>2</sub>)<sub>x</sub>-, or heteroaryl-(CH<sub>2</sub>)<sub>x</sub>-;

10 R<sub>6</sub> is hydrogen, R<sub>7</sub>-CO-, or R<sub>12</sub>-S-;

R<sub>7</sub> is alkyl, substituted alkyl, cycloalkyl-(CH<sub>2</sub>)<sub>y</sub>, aryl-(CH<sub>2</sub>)<sub>y</sub>-, substituted aryl-(CH<sub>2</sub>)<sub>y</sub>- or heteroaryl-(CH<sub>2</sub>)<sub>y</sub>-;

R<sub>8</sub> and R<sub>9</sub> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl-(CH<sub>2</sub>)<sub>y</sub>-, substituted  
15 aryl-(CH<sub>2</sub>)<sub>y</sub>-, heteroaryl-(CH<sub>2</sub>)<sub>y</sub>-;



R<sub>10</sub> is alkyl, substituted alkyl, cycloalkyl-(CH<sub>2</sub>)<sub>y</sub>, aryl-(CH<sub>2</sub>)<sub>y</sub>-, substituted aryl-(CH<sub>2</sub>)<sub>y</sub>- or heteroaryl-(CH<sub>2</sub>)<sub>y</sub>-;

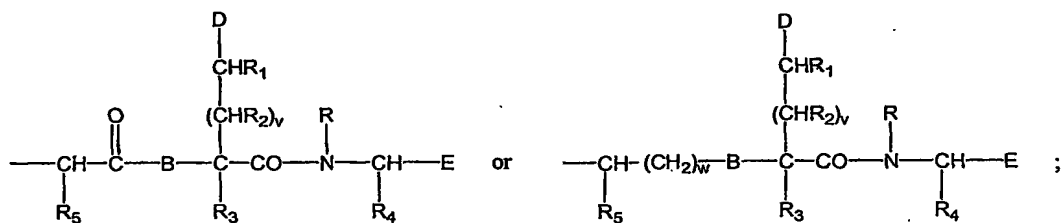
R<sub>11</sub> is hydrogen or lower alkyl; wherein the carbon bearing R<sub>1</sub> and the nitrogen bearing R<sub>11</sub>, when v=1, may be directly  
20 connected together to form an azetidine ring;

R<sub>1</sub> and R<sub>11</sub>, when v=0, may be connected together to form an alkylene bridge of 3 carbon atoms representing with the nitrogen and carbon atoms to which they are attached a piperidine ring;

$R_1$  and  $R_{11}$ , when  $v=1$ , may be connected together to form an alkylene bridge of 2 carbon atoms representing with the nitrogen and carbon atoms to which they are attached a piperidine ring;

$R_2$  and  $R_{11}$ , when  $v=1$ , may be connected together to form an alkylene bridge of 2 carbon atoms representing with the nitrogen and carbon atoms to which they are attached a pyrrolidine ring; the alkylene bridge may be substituted by a lower alkyl or alkenyl group at either carbon;

$R_{12}$  is alkyl, substituted alkyl, cycloalkyl- $(CH_2)_y$ -, aryl- $(CH_2)_y$ -, substituted aryl- $(CH_2)_y$ -, heteroaryl- $(CH_2)_y$ -,



in which case  $-S-R_{12}$  completes a symmetrical disulfide;

$R_{13}$  is hydrogen, lower alkyl, cycloalkyl or phenyl;

$R_{14}$  is hydrogen, lower alkyl, lower alkoxy or phenyl;

$R_{15}$  is lower alkyl or aryl- $(CH_2)_y$ ;

D is  $-\text{COOH}$ ,  $-\text{SO}_2\text{H}$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{PO}_3\text{H}_2$ ;  $-\text{OSO}_3\text{H}$  or  $-\text{OPO}_3\text{H}_2$ ;

E is hydrogen,  $R_{12}$ ,  $-\text{COOH}$ ,  $-\text{CONH}_2$ ,  $-\text{CONH}(\text{lower alkyl})$ ,  $-\text{CON}(\text{lower alkyl})_2$ ,  $-\text{CONH}(\text{CH}_2)_z\text{-aryl}$ ,  $-\text{CON}(\text{CH}_2)_z\text{-aryl}$ ,  $-\text{CO-amino acid}$ ,  $-\text{CH}_2\text{COOH}$ ,  $\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$ , or  $-\text{COOR}_{16}$ ;

$R_{16}$  is as previously defined for  $R_8$  and  $R_9$ ;

C is carbon;

H is hydrogen;

O is oxygen;

N is nitrogen;

S is sulfur;

P is phosphorus;

v is zero or one;

w is zero or an integer ranging from 1 to 4;

5 x is an integer ranging from 1 to 4;

y is zero or an integer ranging from 1 to 6; and

z is zero, one, two or three.

2. The compound as defined in claim 1, which is:

10 N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-  
acetylamino)-succinamic acid;

N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-3-  
phenyl-propionyl amino)-succinamic acid;

N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-  
propionylamino)-succinamic acid;

15 N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-4-  
methyl-pentanoylamino)-succinamic acid;

N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-3-  
methyl-butyrylamino)-succinamic acid;

20 N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(3-hydroxy-2-  
mercapto-propionylamino)-succinamic acid;

N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(3-hydroxy-2-  
mercapto-butyrylamino)-succinamic acid;

N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-  
hexanoylamino)-succinamic acid;

25 N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-4-  
phenyl-butyrylamino)-succinamic acid;

N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-2-  
phenyl-acetylamino)-succinamic acid;

30 3-(3-Biphenyl-4-yl-2-mercapto-propionylamino)-*N*-[1-  
Carboxy-2-(1*H*-indol-3-yl)-ethyl]-succinamic acid;

- 3-(3-(4-Benzoyloxy-phenyl)-2-mercapto-propionylamino)-  
N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-succinamic acid;
- N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-[3-(4-fluoro-  
phenyl)-2-mercapto-propionylamino]-succinamic acid;
- 5 N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-[2-mercapto-3-  
(4-methoxy-phenyl)-propionylamino]-succinamic acid;
- N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(3-cyclohexyl-2-  
mercapto-propionylamino)-succinamic acid;
- N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-[3-(1*H*-indol-3-  
10 yl)-2-mercapto-propionylamino]-succinamic acid;
- N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-3-  
naphthalen-2-yl-propionylamino)-succinamic acid;
- N-(1-Carboxy-2-naphthalen-2-yl-ethyl)-3-(2-mercapto-3-  
phenyl propionylamino)-succinamic acid;
- 15 N-(1-Carboxy-2-hydroxy-ethyl)-3-(2-mercapto-3-phenyl-  
propionyl amino)-succinamic acid;
- N-[1-Carboxy-2-(4-hydroxy-phenyl)-ethyl]-3-(2-  
mercapto-3-phenyl-propionylamino)-succinamic acid;
- N-[1-Carboxy-2-phenyl-ethyl]-3-(2-mercapto-3-phenyl-  
20 propionyl amino)-succinamic acid;
- N-(2-Biphenyl-4-yl-1-Carboxy-ethyl)-3-(2-mercapto-3-  
phenyl-propionyl amino)-succinamic acid;
- N-(1-Benzyl-2-hydroxy-ethyl)-3-(2-mercapto-3-phenyl-  
propionyl amino)-succinamic acid;
- 25 N-[1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-3-  
phenyl-propionylamino)-succinamic acid;
- 4-[1-Carboxy-2-(1*H*-indol-3-yl)-ethylcarbamoyl]-4-(2-  
mercapto-3-phenyl-propionylamino)-ethyl]-butyric acid;
- N-[2-(1*H*-indol-3-yl)-methylcarbamoyl-ethyl]-3-(2-  
30 mercapto-acetyl amino)-succinamic acid;

- N-[1-(1-Carboxy-2-hydroxy-ethylcarbamoyl)-2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-3-phenyl-propionylamino)-succinamic acid;  
 N-[2-(1*H*-indol-3-yl)-methoxycarbonyl-ethyl]-3-(2-mercapto-acetyl amino)-succinamic acid;  
 5 N-[2-(1*H*-indol-3-yl)-ethyl]-3-(2-mercapto-3-phenyl-propionylamino)-succinamic acid;  
 3-(2-Biphenyl-4-yl-ethylcarbamoyl)-4-hydroxycarbamoyl-butyrlic acid;  
 3-[2-(4'-Cyano-biphenyl-4-yl)-ethylcarbamoyl]-4-hydroxycarbamoyl-butyrlic acid;  
 10 4-Hydroxycarbamoyl-3-[2-(4-pyridin-2-yl-phenyl)-ethylcarbamoyl]-butyrlic acid;  
 4-Hydroxycarbamoyl-3-(4-phenyl-butylcarbamoyl)-butyrlic acid;  
 4-Hydroxycarbamoyl-3-(2-phenoxy-ethylcarbamoyl)-butyrlic acid;  
 15 3-[2-(4'-Hydroxy-biphenyl-4-yl)-ethylcarbamoyl]-4-hydroxycarbamoyl-butyrlic acid;  
 3-(2,2-Diphenyl-ethylcarbamoyl)-4-hydroxycarbamoyl-butyrlic acid;  
 20 3-[2-(4'-Dimethylamino-biphenyl-4-yl)-ethylcarbamoyl]-4-hydroxycarbamoyl-butyrlic acid;  
 4-Hydroxycarbamoyl-3-(5-hydroxy-pentylcarbamoyl)-butyrlic acid;  
 25 3-[(Biphenyl-4-ylmethyl)-carbamoyl]-4-hydroxycarbamoyl-butyrlic acid;  
 3-(2-Biphenyl-4-yl-ethylcarbamoyl)-5-hydroxycarbamoyl-pentanoic acid;  
 N-[1-carboxy-2-(1*H*-indol-3-yl)-ethyl]-3-(3-phenyl-1-phosphono-propylamino)-succinic acid; or  
 30

3-(2-Naphthalen-2-yl-ethylcarbamoyl)-pentanedioic acid.

3. The compound of claim 2, which is 3-(2-Biphenyl-4-yl-ethylcarbamoyl)-4-hydroxycarbamoyl-butyric acid.

4. A pharmaceutical composition comprising a  
5 therapeutically effective amount of a compound of any one of claims 1 to 3 and a physiologically acceptable carrier or excipient.

5. A method for inhibiting PHEX comprising contacting PHEX with an inhibitory amount of a compound as recited in any one of claims 1 to 3.

10 6. A method for stimulating bone mass formation in a mammal comprising inhibiting PHEX with an effective amount of a compound as recited in any one of claims 1 to 3.

7. A method for treating or preventing a disease or condition associated with a phosphate metabolism defect comprising  
15 administering an effective amount of a compound as recited in any one of claims 1 to 3 to a mammal in need thereof.

8. A method as recited in claim 7, wherein said disease or condition is selected from the group consisting of hyperphosphatemia, hyperparathyroidism and renal insufficiencies.

20 9. A method for identifying PHEX substrates comprising

contacting a candidate with PHEX in the presence and in the absence of a compound as recited in any one of claims 1 to 3; and

25 assessing PHEX biological activity on the candidate in the presence and in the absence of the compound,

wherein the candidate compound is selected as a PHEX substrate when PHEX biological activity is measurably higher in the absence versus in the presence of the compound.

10. A use of a compound as recited in any one of  
5 claims 1 to 3 for inhibiting PHEX.

11. A use of a compound as recited in any one of  
claims 1 to 3 for stimulating bone mass formation in a mammal.

12. A use of a compound as recited in any one of  
claims 1 to 3 for treating or preventing a disease or condition associated  
10 with a phosphate metabolism.

13. A use of a compound as recited in claim 12,  
wherein said disease or condition is selected from the group consisting of  
hyperphosphatemia, hyperparathyroidism and renal insufficiencies.

14. A use of a compound as recited in any one of  
15 claims 1 to 3, for identifying PHEX substrates comprising  
contacting a candidate with PHEX in the presence and in  
the absence of the compound; and

assessing PHEX biological activity on the candidate in the  
presence and in the absence of the compound,

20 wherein the candidate compound is selected as a PHEX  
substrate when PHEX biological activity is measurably higher in the  
absence versus in the presence of the compound.